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Estimands for Overall Survival in clinical trials with treatment switching

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Estimands in clinical trials with treatment switching

- On behalf of the Treatment Switching subteam of the **European special interest group "Estimands in oncology"**
- **Sponsoring** by PSI and EFSPI and ASA scientific working group of the ASA biopharmaceutical section
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- **More information:** www.oncoestimand.org

Declarations

Title: *Estimands in clinical trials with treatment switching*

Authors: *Juliane Manitz, Hannes Buchner et al.*

DOI: *Manuscript submitted: "Estimands for Overall Survival in Clinical Trials with Treatment Switching"*

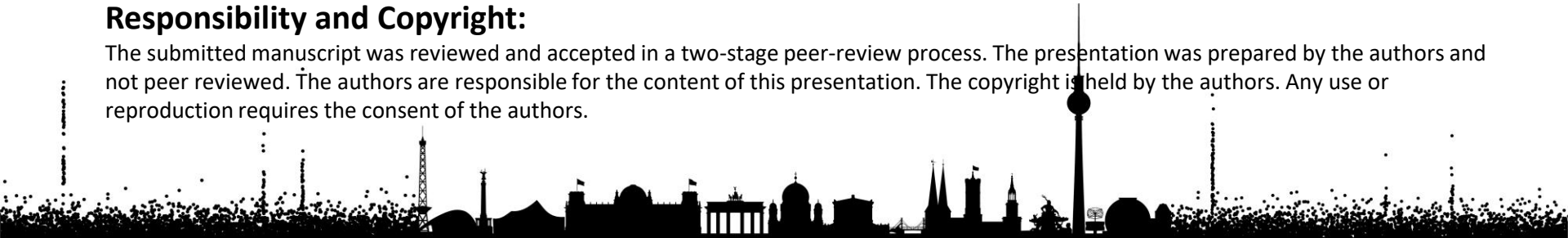
Conflict of Interest:

- *Employment of (co-)authors*
- *See previous slide*

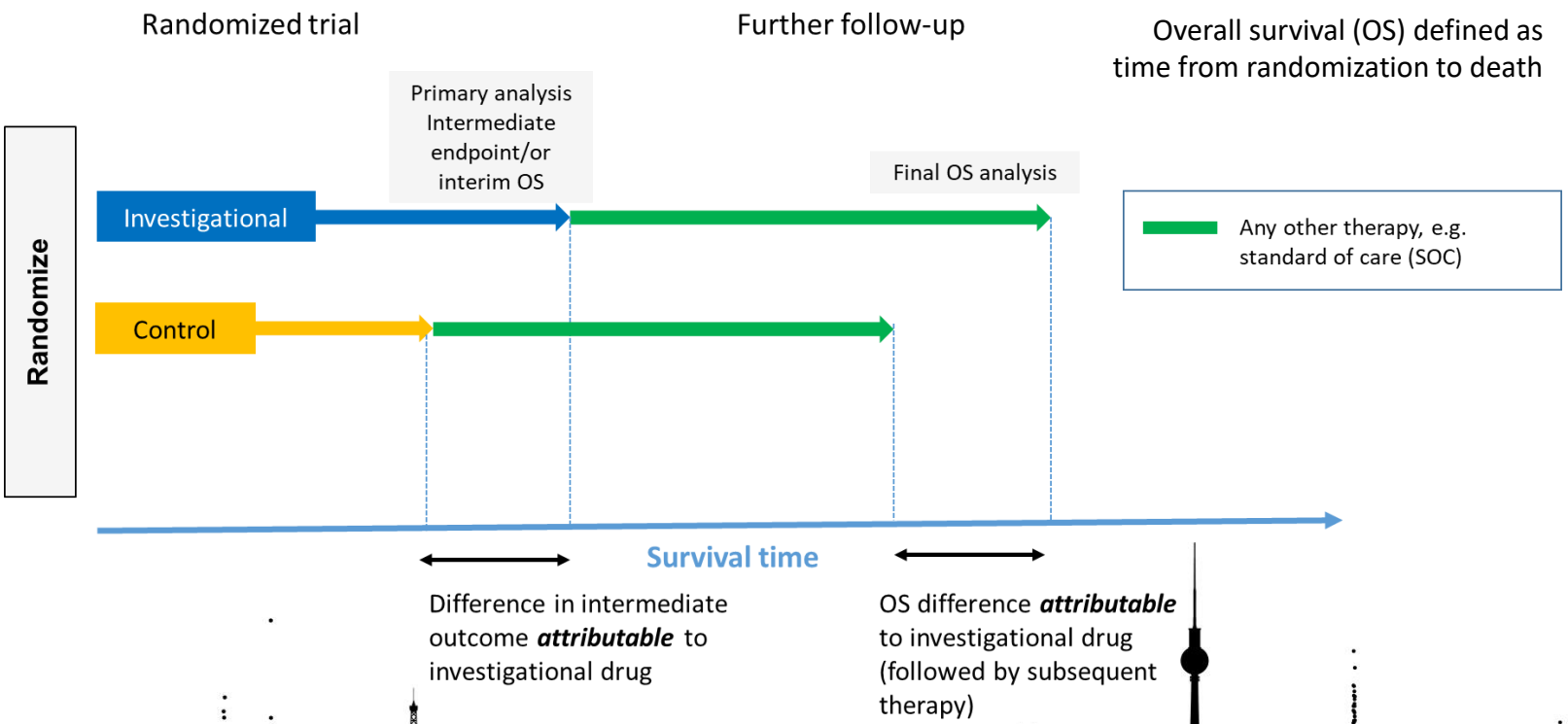
Ethics Comittee an Preregistration :

- Ethics vote: *N/A*
- Preregistration: *N/A*

Responsibility and Copyright:

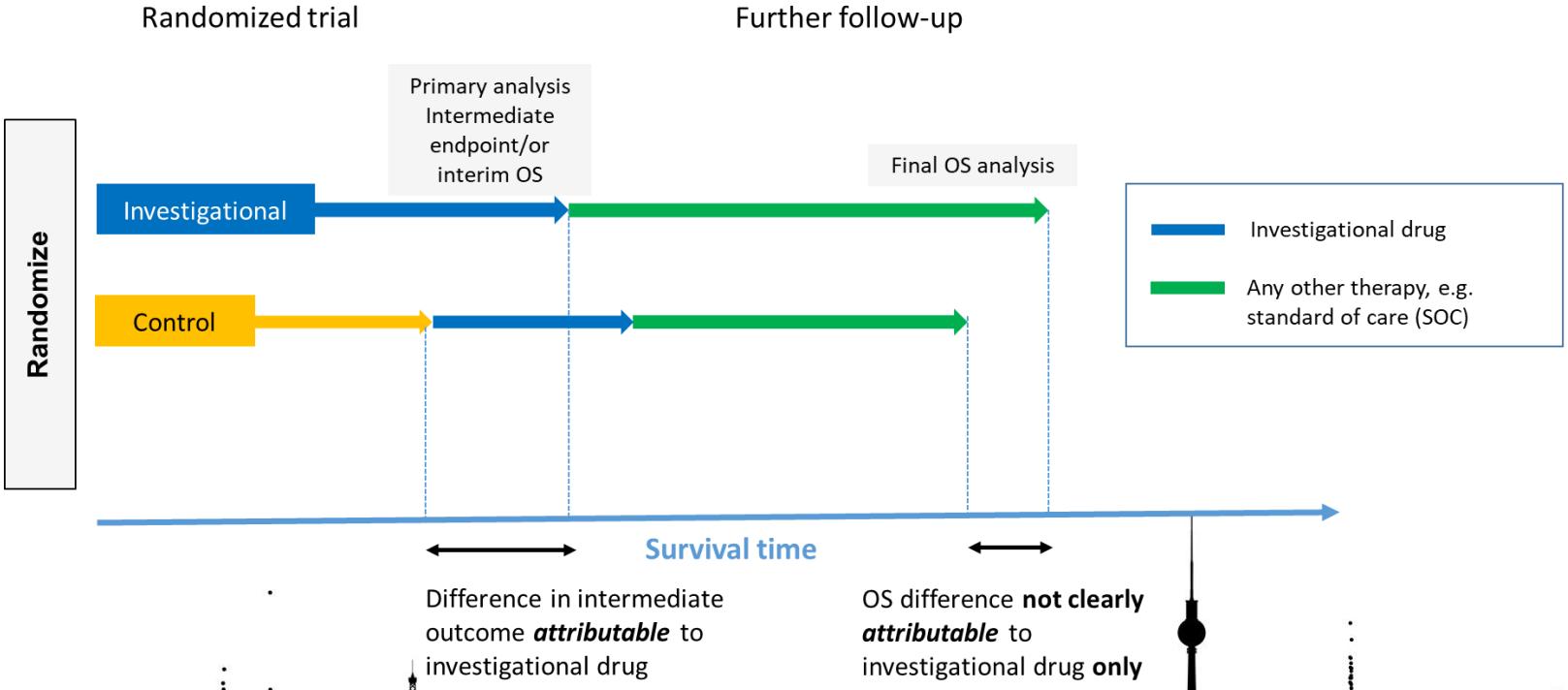


A Stylized Example of a Randomized Clinical Trial in Oncology



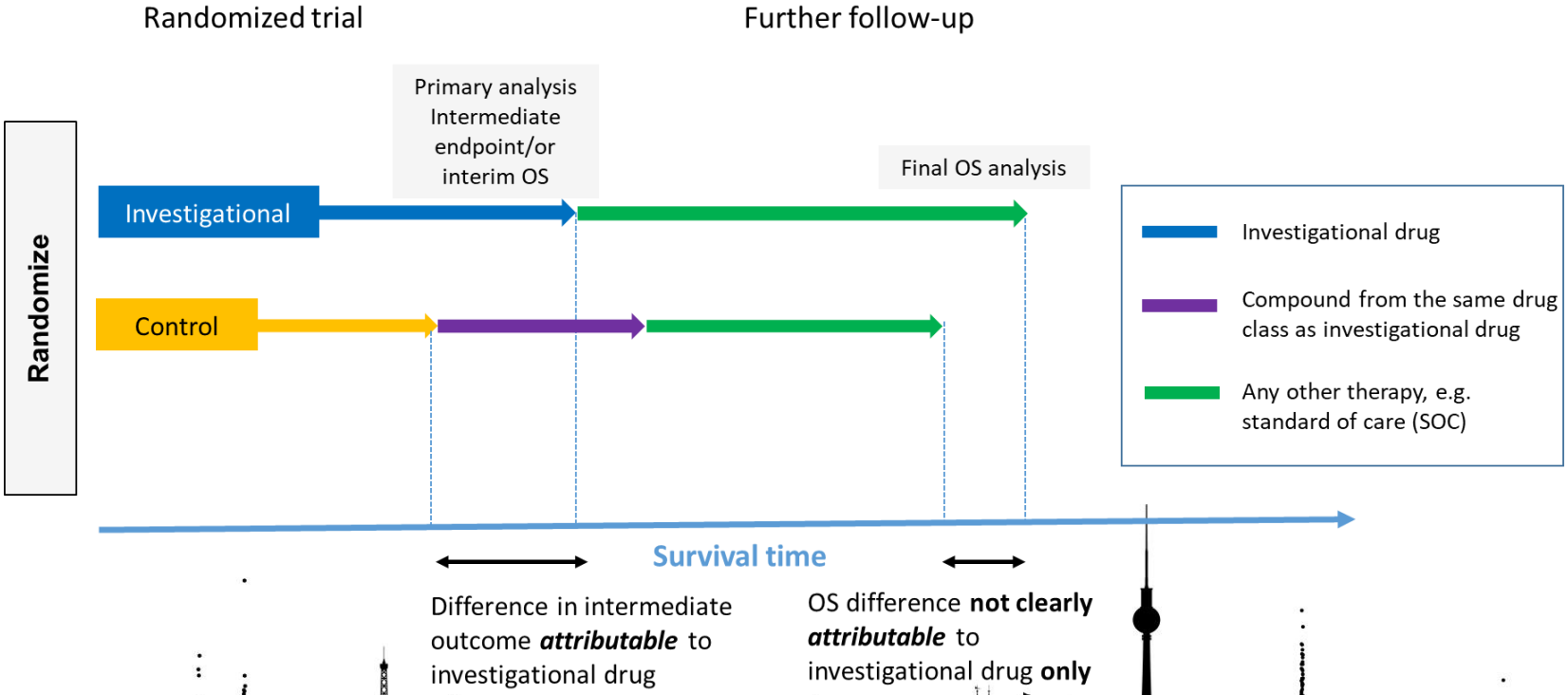
Treatment Switching Scenario 1:

Cross-over from Control to Investigational Arm



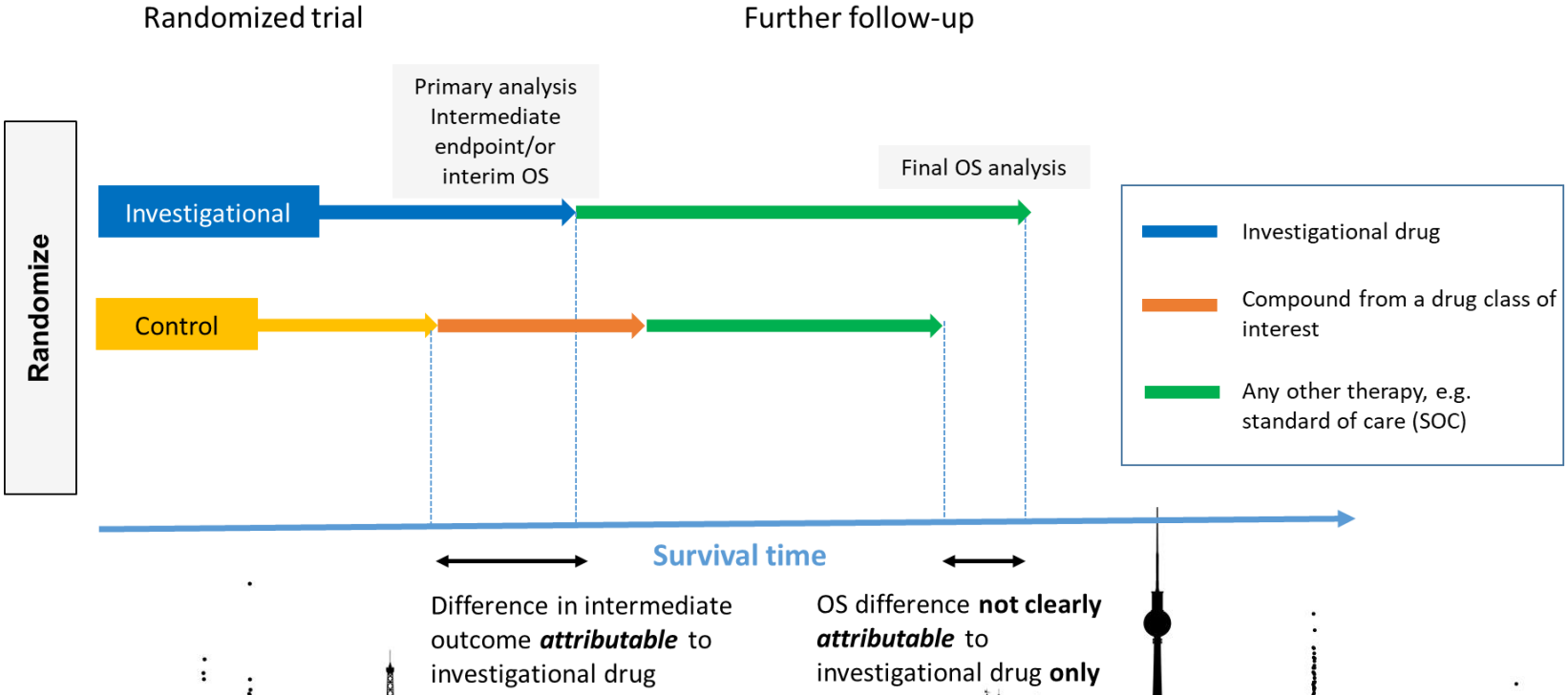
Treatment Switching Scenario 2:

From Control to Same Drug Class as of Investigational Arm

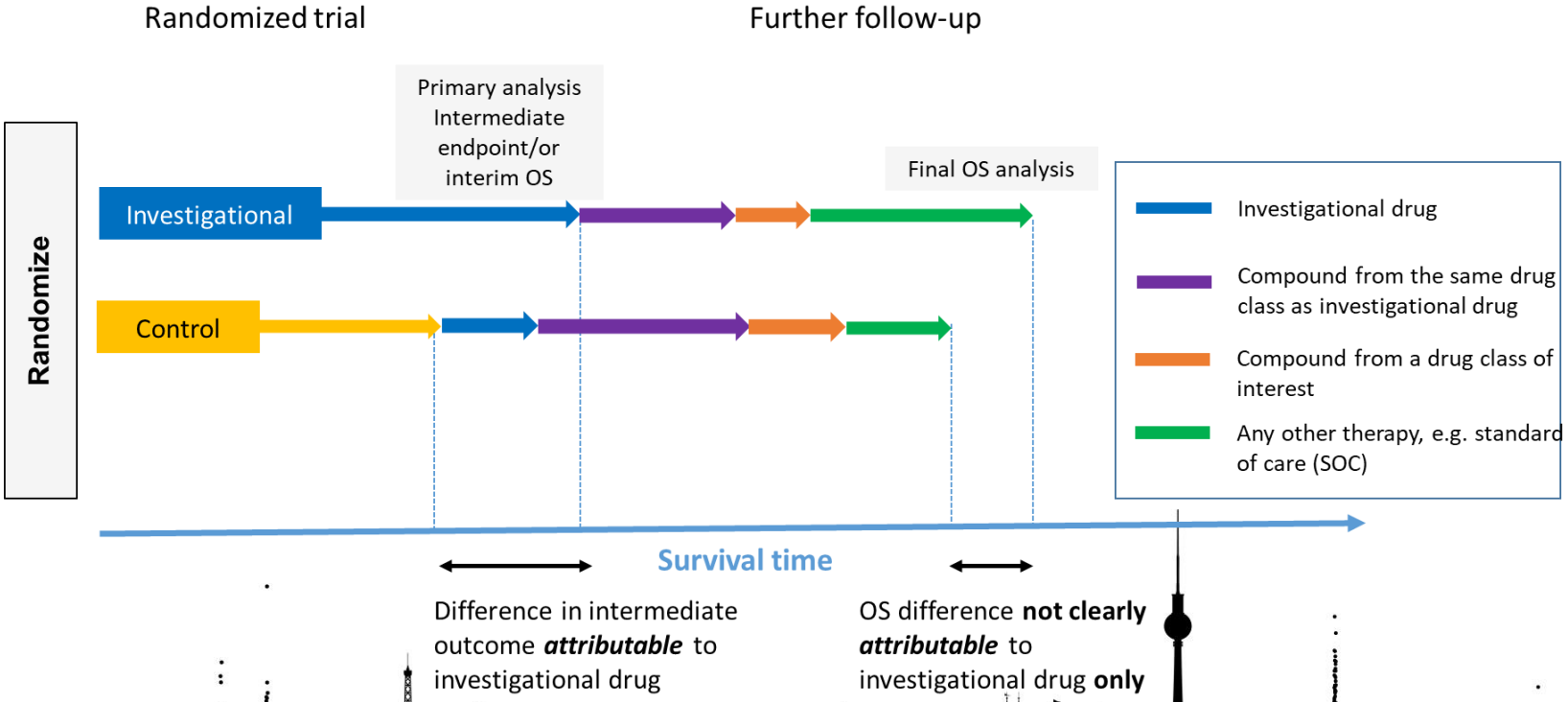


Treatment Switching Scenario 3:

From Control Arm to Drug Class of Interest



A More Realistic Example:
Mix of Treatment Switching Scenarios



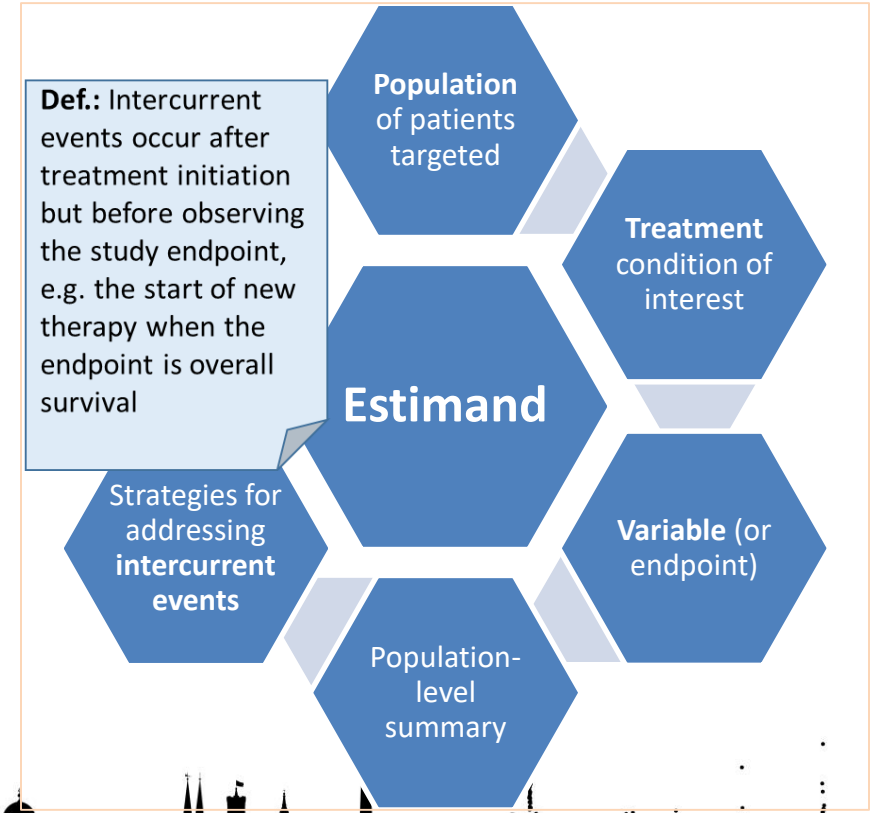
What do we actually measure? What are the key questions?

- The traditional approach ignores treatment switching and rest on the following assumptions:
  - ✓ Subsequent therapy reflect clinical practice (including investigational drug in later line) **in particular decision context**
  - ✓ Patients receiving subsequent treatments (from same class as investigational drug and drug class of interest) and dose intensity as expected (as SOC) between investigational and control arm
- If these assumptions do not hold, we may consider to estimate the OS benefit that is attributable to the investigational drug
- The estimand framework provides a coherent framework to make the arising issues of treatment switching explicit and offers a systematic and transparent approach for assessment

What is an Estimand?

- **Estimand** is the target of estimation to address the scientific question of interest posed by the study objective.
- An estimand is described by five attributes, defining together the treatment effect of interest.

- ➢ Align trial **objectives** and statistical analyses by requiring a precise definition of the population quantity of interest
- ➢ Increase transparency with respect to data analysis and inference
- ➢ Strengthen the dialogues between disciplines involved in the formulation of clinical study objectives, design, conduct, analysis and interpretation

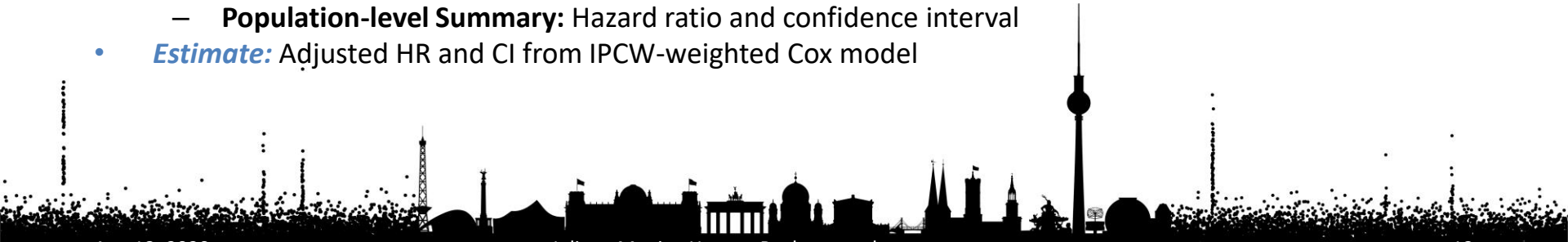


Treatment Policy Estimand

- ***Objective:*** Evaluate OS benefit assuming subsequent therapies represent clinical practice
- ***Estimand:***
  - **Population:** Defined through appropriate I/E criteria to reflect the target patient population for approval
  - **Variable:** Overall survival, defined as the time from randomization to death
  - **Treatment:** Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapies (including Investigational drug)
  - **Handling of intercurrent events:**
    - Start of subsequent therapy at any time: Treatment policy
    - Crossover to investigational drug at any time: Treatment policy
    - Crossover to investigational drug at disease progression: Treatment policy
  - **Population-level Summary:** Hazard ratio and confidence interval
- ***Estimate:*** Cox model and KM estimates using ITT approach

Hypothetical Estimand

- ***Objective:*** Evaluate OS benefit adjusted for treatment switching
- ***Estimand:***
  - **Population:** Defined through appropriate I/E criteria to reflect the target patient population for approval
  - **Variable:** Overall survival, defined as the time from randomization to death
  - **Treatment:** Investigational drug vs control (if there were no subsequent therapies)
  - **Handling of intercurrent events:**
    - Start of subsequent therapy at any time: Hypothetical
    - Crossover to investigational drug at any time: Hypothetical
    - Crossover to investigational drug at disease progression: Hypothetical
  - **Population-level Summary:** Hazard ratio and confidence interval
- ***Estimate:*** Adjusted HR and CI from IPCW-weighted Cox model



Estimands in Clinical Trials with Treatment Switching

OBJECTIVE	*Evaluate OS benefit assuming subsequent therapies represent clinical practice*	*Evaluate OS benefit adjusted for treatment switching*	*Evaluate OS benefit adjusted for treatment crossover*	*Evaluate OS benefit adjusted for treatment crossover at disease-related time-point*
ESTIMAND				
Population	Defined through appropriate I/E criteria to reflect the target patient population for approval			
Variable / Endpoint	Overall survival: Time from randomization to death			
Treatment condition of interest	Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapies (including Investigational drug)	Investigational drug vs control (if there were no subsequent therapies)	Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapy (excluding investigational drug)	Sequence of Investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapy (excluding investigational drug)
Handling of intercurrent events (IEs)				
IE: Start of subsequent therapy at any time	Treatment policy	Hypothetical	Treatment policy	Treatment policy
IE: Crossover to investigational drug at any time	Treatment policy	Hypothetical	Hypothetical	Treatment policy
IE: Crossover to investigational drug at disease progression	Treatment policy	Hypothetical	Hypothetical	Hypothetical
Population-level Summary	Kaplan – Meier estimates; Hazard ratio (HR) with confidence interval (CI)			
ESTIMATION	Cox model and KM estimates using ITT approach	Adjusted HR and CI from IPCW-weighted Cox model; weighted KM estimates	HR from RPSFT model using adjusted survival times; IPCW methods could also be used	HR from two-stage method using reconstructed survival; IPCW and RPSFT methods could be used

Conclusions & Summary

- Treatment policy estimand may not be clinically relevant if subsequent therapy does not represent clinical practice
- The estimand framework provides a coherent framework to make the issues of treatment switching explicit and offers a systematic and transparent approach for assessment
- Start to think about possible treatment switching scenarios during the planning phase of a trial
- Choose appropriate estimand according to pre-specified scientific question of interest
- Treatment switching methods which can be applied if the necessary data is collected; assumptions apply

Further reading: The corresponding manuscript is submitted: “Estimands for Overall Survival in Clinical Trials with Treatment Switching”